UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/453,801	12/03/99	CHATTERJEE S	1954-287

HM12/0718

MARTHA CASSIDY
ROTHWELL FIGG ERNST & KURZ
SUITE 701 EAST
555 13TH STREET NW
WASHINGTON DC 20004

EXAMINER	
LEFFERS JR, G	
ART UNIT	**PAPER NUMBER**
1636	9

DATE MAILED: 07/18/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/453,801	CHATTERJEE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *27 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33* is/are pending in the application.

4a) Of the above claim(s) *24-33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 1999* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5,6* .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Receipt is acknowledged of an Information Disclosure Statement, filed 3/3/00 as Paper No. 5. Receipt is also acknowledged of a supplementary Information Disclosure Statement, filed 5/16/00 as Paper No. 6. The corresponding signed and initialed PTO-1449 forms have been mailed with this action.

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-23) in Paper No. 8 is acknowledged. Claims 1-33 are pending in this application, with claims 24-33 being withdrawn from consideration as being drawn towards nonelected inventions.

Drawings

This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed. Applicants' attention is also directed towards the comments from the draftsperson communicated on the Form PTO 948 mailed with this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6, 11-14, 22-23 are rejected under 35 U.S.C. 102(a) as being anticipated by Wong et al (Blood. November 1998, Vol. 92, No. 10, Suppl. 1, Abstract #2738; see the entire document).

Wong et al teach methods of gene transfer into quiescent CD34+CD38- hematopoietic progenitor cells with AAV vectors. Wong et al teach that Hoeschst 33342 and Pyronin Y staining followed by flow cytometric sorting was used to purify CD34 cells in the G0 phase from a population of $CD34^+$ $CD38^-$ cells. Staining assays demonstrated that selected cells in G0 phase and grown in low cytokine conditions proliferated more slowly than cells in G1 under the same conditions. Target cells were transduced with an AAV vector comprising sequences encoding an HIV LTR antisense oligonucleotide. Transduced $CD34^+$ cells in G0 were found to be enriched for LTC-IC cells with extended clonogenic capacity while cells in G1 were found to have very limited LTC-IC activity. The authors found that 7-30% of the CD34 cells in G0 contained chromosome-associated vector-specific signals in metaphase spreads.

Claims 1-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Fisher-Adams et al (Blood. 1996, Vol. 88, No. 2, pages 492-504; see the entire document).

Fisher-Adams et al teach the construction and use of AAV vectors for transduction of human bone marrow or umbilical cord $CD34^+$ hematopoietic progenitor cells (Abstract). The $CD34^+$ cell population was obtained by selection with anti-$CD34^+$ antibody and $CD34^+$ purity of the cells obtained was estimated to be approximately 70-95% as determined by

direct immunoflouresence with flourescein isothiocyanate-conjugated HPCA-2. AAV vectors used in the transduction experiments were vCWRAP, vCWRHIVA-PAP and vCWRHIVASVN. Each of these vectors comprises the AAV ITR sequences, AAV polyadenylation and RNA termination sequences (e.g. Figure 1). Transduction times are not explicitly defined in the reference, although the transduction and culture conditions appear to have been identical. In at least one experiment, the cells are described as being transduced and cultured for 24 hours, followed by washing with 1 X PBS to remove any non-transduced viral particles. Transduction was performed with and without prior stimulation of the selected $CD34^+$ cells with cytokines. The cells were maintained in culture media comprising: IL-3 at 10 ng/ml, IL-6 at 5 ng/ml and granulocyte-macrophage stimulating factor at 1 ng/ml (Materials and Methods). The relative transduction efficiencies indicate that "cytokine-mediated induction of proliferation and/or differentiation was not obligatory for AAV transduction (page 502, column 1, lines 1-6). The authors confirmed stable integration of the AAV vectors into the $CD34^+$ cell population by FISH analysis of metaphase cells and Southern analysis (e.g. page 502, column 2, last paragraph).

The method of initially selecting the $CD34^+$ cell population described by Fisher-Adams et al, anti-CD34 antibody-mediated selection, is essentially the same means of initial selection applied by applicants for selection of their population of quiescent $CD34^+$ cells. Further, the media described by Fisher-Adams et al for culturing and transduction of their $CD34^+$ hematopoietic progenitor cells was the same "low cytokine" media as described by applicants as maintaining the selected cells in a quiescent state. Therefore, one of skill in the art would necessarily expect that within the population of $CD34^+$ cells described by Fisher-Adams et al there would be a sub-population of quiescent $CD34^+$ cells residing in the G0 phase of the cell

cycle which would remain in a quiescent state for the duration of transduction. Moreover, one of skill in the art would necessarily expect that the population of hematopoietic progenitor cells isolated by Fisher-Adams et al would have a further subset of cells having the $CD34^{+++}$ $CD38^{-}$ characterization for the same reasons.

Because the Office does not have the facilities for examining and comparing the applicant's product (i.e. the $CD34^{+}$ cell population residing in the G0) with the products of the prior art (i.e. the $CD34^{+}$ cells isolated by Fisher-Adams et al), the burden is on the applicant to show a novel or unobvious difference between the claimed product and the products of the prior art (e.g. that the products of the prior art does not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1-6, 11-15, 22-23 are rejected under 35 U.S.C. 102(b) as being anticipate by Zhou et al (J. Exp. Med. 1994, Vol. 179, pages 1867-1875; see the entire document).

Zhou et al teach methods of gene transfer into immature and mature subsets of hematopoietic progenitor cells obtained from human umbilical cord blood wherein the gene transfer is mediated by AAV-2 vectors (Abstract). The AAV-2 vectors described by the reference comprise the viral ITR sequences flanking a gene of interest (e.g. neo^{r}). The $CD34^{+}$ cell population used as target cells for transduction was isolated from low-density mononuclear cord blood cells following ultra-centrifugation. The CD34+ cells were selected via specific binding to a CD34-specific antibody. The cells were infected for 2 hours at 37C in media comprising "low levels" of cytokines (i.e. 100U/ml epo, 100 U/ml IL-3, 100 U/ml of GM-CSF).

Cells were either pre-stimulated or not stimulated with growth factors prior to transduction (Materials and Methods). Pre-stimulation with cytokines did not significantly enhance the rates of transduction (e.g. Abstract; page 1872, column 1, first paragraph). The reference further teaches that in prior art experiments featuring retroviral vectors, "...cord blood cells were first exposed to potent combinations of growth factors to place the progenitors into a higher cell cycle state before exposing the cells to the retroviral vectors. In contrast, the data presented herein demonstrate high efficiency transduction into slow or noncycling [examiner's emphasis] immature and mature human hematopoietic progenitors from cord blood in the absence of growth factor stimulation using the recombinant AAV-based vector system without further enhancement, even when the cells are prestimulated with growth factors." This teaching indicates the authors themselves considered the population of transduced CD34+ cells to comprise cells which were "noncycling" or quiescent.

The method of initially selecting the $CD34^+$ cell population described by Zhou et al, anti-CD34 antibody-mediated selection, is essentially the same means of initial selection applied by applicants for selection of their population of quiescent $CD34^+$ cells. Further, the media described by Zhou et al for culturing and transduction of their $CD34^+$ hematopoietic progenitor cells is a "low cytokine" media. Therefore, one of skill in the art would necessarily expect that within the population of $CD34^+$ cells described by Zhou et al there would be a sub-population of quiescent $CD34^+$ cells residing in the G0 phase of the cell cycle which would remain in a quiescent state for the duration of transduction. Moreover, one of skill in the art would necessarily expect that the population of hematopoietic progenitor cells isolated by Zhou

et al would have a further subset of cells having the $CD34^{+++}$ $CD38^{-}$ characterization for the same reasons.

Because the Office does not have the facilities for examining and comparing the applicant's product (i.e. the $CD34^{+}$ cell population residing in the G0) with the products of the prior art (i.e. the $CD34^{+}$ cells isolated by Zhou et al), the burden is on the applicant to show a novel or unobvious difference between the claimed product and the products of the prior art (e.g. that the products of the prior art does not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claims 1-4, 6-7, 11-15, 22-23 are rejected under 35 U.S.C. 102(b) as being anticipated by Luhovy et al (Biology of Blood and Marrow Transplantation. 1996, Vol. 2, pages 24-30; see the entire document).

Luhovy et al teach the stable introduction of genes into human hematopoietic stem cells via transduction of the target cells with an AAV vector. Following infection, at least one portion of the selected cells was cultured for six weeks under conditions that maintain long-term culture-initiating cells (LTC-IC). The authors teach that their results demonstrate for the first time that LTC-IC cells can be transduced stably with a recombinant AAV vector (e.g. Abstract). Hematopoietic progenitor cells were isolated from bone marrow via density gradient centrifugation and CD34+ cells were selected by specific binding to anti-CD34 antibodies to generate CD34+ cell populations having ~90% purity. These cell populations were further selected for CD34+ Lin- phenotypes by two- or three-color FACS with anti-CD34, anti-Lin

(CD3, CD14, CD19, CD56) and anti-Thy antibodies (Materials and Methods). The AAV vector used for transduction comprises the AAV ITR sequences flanking the gene of interest and was packaged into AAV virions in a modified HeLa packaging cell line (Materials and Methods). Isolated target cells were transduced in RPMI and incubated for 14 hours at 37C prior to washing 3X with PBS to remove non-transduced virions.

The method of initially selecting the $CD34^+$ cell population described by Luhovy et al, anti-CD34 antibody-mediated selection, is essentially the same means of initial selection applied by applicants for selection of their population of quiescent $CD34^+$ cells. Further, Luhovy et al describe further rounds of selection to isolate cells lacking cell differentiation markers (i.e. Lin- Thy- cells). The transduction conditions described by Luhovy et al lack any pre-stimulation of the target cells with cytokines and further lack the presence of such cytokines in the transduction media. Therefore, one of skill in the art would necessarily expect that within the population of $CD34^+$ cells described by Luhovy et al there would be a sub-population of quiescent, immature $CD34^+$ cells residing in the G0 phase of the cell cycle which would remain in a quiescent state for the duration of transduction. This is confirmed by the showing that stably transduced LTC-IC cells were observed more than six weeks following transduction. Moreover, one of skill in the art would necessarily expect that the population of hematopoietic progenitor cells isolated by Zhou et al would have a further subset of cells having the $CD34^{+++}$ $CD38^-$ characterization for the same reasons.

Because the Office does not have the facilities for examining and comparing the applicant's product (i.e. the $CD34^+$ cell population residing in the G0) with the products of the prior art (i.e. the $CD34^+$ cells isolated by Luhovy et al), the burden is on the applicant to show a

novel or unobvious difference between the claimed product and the products of the prior art (e.g. that the products of the prior art does not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 23 are vague and indefinite in that the metes and bounds of the term "stably transfecting" are unclear. The term does not appear to be explicitly defined in the specification and is inherently indefinite. How many generations does the transferred DNA have to be present in the transduced cell for it to be considered "stably" transferred? It would be remedial to amend the claim language to clearly indicate what is intended by the limitation of "stably transferring" a DNA into the target cells.

Claim 2 is vague and indefinite in that the metes and bounds of the phrase "...the cells in G0 phase do not differentiate or undergo mitosis substantially during the transduction process" are unclear. What level of differentiation or mitotic activity within the target cell population would constitute "substantial" activity? It would be remedial to amend the claim

language to more clearly indicate what constitutes "substantial" cell differentiation or mitotic activity for the transduced cell population.

Claims 3-5, 7-10 are vague and indefinite in that the claims comprise the term "about" applied to the duration of the transduction period or to the concentration of various cytokines in the transduction media. The term "about" doesn't appear to be explicitly defined in the specification with regard to these transduction variables and is inherently indefinite. For example, would a transduction period of 30 hours constitute "about" 24 hours? Would an IL-3 concentration of 35 ng/ml constitute "about" 15 ng/ml? It would be remedial to amend the claim language to more precisely indicate what are the actual boundaries encompassed by the term "about".

Claim 6 is vague and indefinite in that the metes and bounds of the term "low cytokine levels" are unclear. Although the specification lists preferred levels for three cytokines, it is not clear that the term "low cytokine levels" has been explicitly defined by this information. Also, it is not clear how the term would apply to other cytokines not addressed by the specification. It would be remedial to amend the claim language to clearly indicate what is intended by the cited term.

Claims 12-13 are vague and indefinite in that the metes and bounds of the term "capable of" are unclear. Under what conditions are the transferred DNAs supposed to be "capable of" remaining integrated into the genome of the target host cells? It would be remedial to amend the claim language to more clearly define under what conditions the integrated DNAs are "capable of" remaining integrated into the host cell genome.

Claim 14 is vague and indefinite in that the metes and bounds of the term "$CD34^{+++}$" are unclear. The specification does not clearly define what constitutes a $CD34^{+++}$ cell as opposed to a $CD34^{+++}$, nor does the designation $CD34^{+++}$ appear to be uniformly applied in the prior art. It would be remedial to amend the claim language to more clearly define what constitutes a "$CD34^{+++}$" cell.

Claim 16 is vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to generate an AAV vector "derivative" of the vector CWRSV".

Claim 23 is vague and indefinite in that the phrase "...which comprises transducing said multi-potential hematopoietic stem cells.." is repeated consecutively in the body of the claim.

Conclusion

No claims are allowed.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald Leffers , Jr. whose telephone number is (703) 308-6232.

The examiner can normally be reached on Monday through Friday, from about 9:00 AM to about 5:30 PM. A phone message left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Rob Schwartzman, Ph.D., can be reached at (703) 308-7307.

Any inquiry of a general nature or relating to the status of this application, or relating to attachments to this office action, should be directed to the Patent Analyst Zeta Adams, whose telephone number is (703) 305-3291.

GLJ

G. Leffers Jr., Ph.D.

Patent Examiner

Art Unit 1636

13 July 2001

DAVID GUZO
PRIMARY EXAMINER